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EXAMINER	
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ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/099,895	GUTHRIDGE ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 2/2/07 has been entered in full. Claims 73-75, 78 and 79 are amended. Claims 1-72 were canceled previously.

Claims 73-79 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

The following page numbers refer to the previous Office Action (10/2/06).

The objection to the specification at pg 2-3 are *withdrawn in part* in view of Applicants' amendments to the specification. Specifically, Applicants have submitted a substitute specification that correctly identifies the binding motif HSRSLP as residues 598-603 of SEQ ID NO: 1 and therefore this basis for objection is moot. However, please note that the objection to the specification for lack of a descriptive title has been maintained (see below).

The rejection of claims 73-79 under 35 U.S.C. § 112, first paragraph at pg 3-7 for failing to provide enablement for the full scope of the claims is *withdrawn in part* in view of Applicants' amendments to the claims. Specifically, the claims have been amended to limit the claimed methods to "inhibiting hematopoietic cell survival"; therefore the basis of the rejection for encompassing "increasing hematopoietic cell survival" is moot in view of the amended claims. However, please note that the rejection has been maintained (see below) with regard to (1) other mutations of the binding motif and (2) inhibiting hematopoietic cell survival in vivo.

The rejection of claims 73-79 under 35 U.S.C § 112, second paragraph, at pg 7-8 for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is *withdrawn in part* in view of Applicants' amendments to the claims. Please see below for the portion of the rejection that is maintained.

The rejection of claims 73-79 under 35 U.S.C. § 102(a) as being clearly anticipated by Stomski et al (1999) at pg 8-9 is *withdrawn* in view of the "Declaration Of Mark Andrew Guthridge, Michael Claude Berndt, Frank Charles Stomski, and Angel

Francisco Lopez Under 37 C.F.R. § 1.132 And In Accordance With *In Re Katz*" filed 2/2/07, which is sufficient to overcome the rejection.

Maintained Objections and/or Rejections

Claim Objections

The disclosure is objected to because of the following informalities:

The current title of the invention, "METHOD OF REGULATING HEMATOPOIETIC CELL SURVIVAL" is not descriptive, because it encompasses activation or enhancement of cell survival, and the claims are limited to methods of inhibiting cell survival. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: "METHOD OF INHIBITING HEMATOPOIETIC CELL SURVIVAL".

Applicants' arguments (2/2/07; pg 4) as they pertain to the objection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants submit that a substitute specification has been submitted that includes the title suggested by the Examiner in the previous Office Action (10/2/06; pg 3).

Applicants' arguments have been fully considered but are not found persuasive. The title suggested by the Examiner related to the previously pending claims, which were directed to a method of "regulating" hematopoietic cell survival. Applicants have currently amended the claims to limit them to a method of "inhibiting" hematopoietic cell survival. "Inhibiting" cell survival is narrower in scope than "regulating" cell survival, which additionally encompasses activating or enhancing cell survival. Therefore, the title is not descriptive because it is not clearly indicative of the invention to which the claims are directed. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 73-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of decreasing hematopoietic cell survival in vitro comprising mutating the sequence HSRSLP (residues 598-603) of SEQ ID NO: 1 to EFAAAA (or by truncating the receptor as taught by the prior art) does not reasonably provide enablement for (1) other mutations of the binding motif or (2) a method of inhibiting hematopoietic cell survival in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection was set forth at pg 3-7 of the 10/2/06 Office Action.

Applicants' arguments (2/2/07; pg 4-6) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

With respect to an in vivo method of inhibiting cell survival in vivo, Applicants submit that *in vitro* activity as measured by the assay in Example 8 is predictive of *in vivo* activity. Applicants submit that the same part of the cell signaling transduction pathway is effected in each instance. Applicants point to the 6/20/06 Response at pg 5 as describing the cell survival pathway. Applicants submit that Example 4 also shows that mutation of the claimed binding motif results in *in vivo* inhibition of phosphorylation required for signal transduction that in turn inhibits cell survival.

Applicants' arguments have been fully considered but are not found persuasive. There are no working examples or other evidence in the specification indicating that the *in vitro* activity measured by the assay in Example 8 is predictive of *in vivo* activity. Even if the cell signaling transduction pathway may potentially be the same in each case, the extracellular conditions of cells grown *in vitro* (e.g., in culture) are very different from the condition of cells grown *in vivo* (e.g., in an organism) and may effect the phenotype of cell survival in an unpredictable way. For example, both the instant specification (pg 45,

lines 21-23) and the relevant art (Guthridge et al (2000); cited previously) teach that CTL-EN cells expressing the mutant receptor show no defect in cell survival when grown in 10% FCS (fetal calf serum). This example demonstrates that the survival of hematopoietic cells expressing the mutant receptor is sensitive to the environment (extracellular conditions). Therefore, it is maintained that the skilled artisan could not predict whether or not mutation of the HSRSLP binding motif would result in decreased hematopoietic cell survival *in vivo*. Furthermore (as set forth previously) the claimed methods encompass in vivo methods of regulating hematopoietic cell survival. Such methods include both administration of genetically altered hematopoietic cells to an animal, or transgenic animals expressing altered hematopoietic cells (in either case, the hematopoietic stem cells have a β chain with an altered HSRSLP binding motif). However, there are no methods or working examples disclosed in the specification for administration of hematopoietic cells, or creation of transgenic multicellular animals, that express the mutant receptor. While Applicants submit that Example 4 teaches *in vivo* inhibition of phosphorylation by mutation of the binding motif, this example actually teaches inhibition of phosphorylation in transfected HEK 293T cells in culture. Therefore, this example does not provide any teaching regarding *in vivo* cell survival in an organism.

With respect to the scope of the mutations encompassed by the claimed methods, Applicants submit that the skilled artisan would have been able to create the claimed binding motif mutations using methods already generally known in the art; in support Applicants point to Example 1(a) pg 35, lines 15-28. Applicants argue that *In re Vaeck* (1991) supports that Applicants need not disclose every species encompassed by their claims, such as the details regarding construction of the mutated binding motifs. Applicants further argue the specification describes assays that can be used to determine whether a mutated binding motif disrupts binding such that cell survival is affected; Applicants point the specification at pg 21, lines 28-34 and Example 8-9 on page 46-48.

Applicants' arguments have been fully considered but are not found persuasive.

The examiner does not dispute Applicants' characterization of *In re Vaeck* (1991) as holding that Applicants need not disclose every species encompassed by their claims. However, the instant claims are directed to methods encompassing use of a genus of receptors with at least one mutation in the bind HSRSLP binding motif (residues 598-603 of SEQ ID NO: 1). The binding motif consists of six residues that can be altered either singly or in combination. Potential mutations include substitutions, deletions or additions; furthermore, other residues outside of the binding motif may be altered in conjunction. For example, the prior art teaches that a truncated β-chain ending at residue 541 does not support growth of transfected CTLL2 hematopoietic cells.

Considering only substitutions within the binding motif there are 20 amino acids possible at each of six positions, which represents a genus of approximately 20^6 (6.4×10^7) different mutant binding motifs encompassed by the claims. Applicants teach that a single species of mutant motif (EFAAAA) within this vast genus results in decreased cell survival. It is not predictable which other mutations (either single mutations or combinations thereof) at residue 598 (histidine), 599 (serine), 600 (arginine), 601 (serine), 602 (leucine), or 603 (proline) will result in an alteration in cell survival. Changes in as little as a single amino acid residue within this region can have deleterious effects on the expressed protein. Stomski et al (1999; cited previously) teaches that "Experiments examining the association of the β_c-585S→A point mutation with GST-14-3-3 were not possible because it is likely that this mutation introduced a cryptic proteolysis cleavage site. Flow cytometry and Western blot analysis indicated that this mutant was proteolysed and failed to be expressed on the cell surface" (pg 1937). Furthermore, the single species (EFAAAA) tested by Applicants represents a change to each of the residues within this region. The effects of mutations are often additive in combination (see Wells, 1990; cited previously). Therefore, it is not predictable whether not changes that alter less than all six residues will also result in decreased cell survival.

Therefore, it is maintained that the claims encompass numerous embodiments wherein it is unpredictable whether or not the claimed method will function. Furthermore, the combination of these unpredictable embodiments (specifically, the

nature of the mutation and the ability to regulate cell survival *in vivo* in an organism) results in an extremely large genus of embodiments with unpredictable functionality. Due to the large quantity of experimentation necessary to determine if the claimed method could be used to regulate hematopoietic cell survival over the full scope of the claims, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 73-79 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As set forth previously, Claim 73 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a method step(s) wherein the survival of a hematopoietic cell is regulated. Therefore, the method steps do not achieve the goal of the preamble of "inhibiting hematopoietic cell survival". The remaining claims are rejected for depending from an indefinite claim.

Applicants' arguments (2/2/07; pg 6) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that that the specification (pg 47, lines 31-32 and Example 4) explains that the claimed mutation inhibits cell survival by inhibiting the phosphorylation required for signal transduction.

Applicants' arguments have been fully considered but are not found persuasive.

The teachings of the specification with regard to the claimed invention have been fully considered but are not sufficient to overcome the rejection. In the specification, the mutation is made to the protein by constructing a DNA sequence encoding the mutated protein and transfecting said sequence into cells. The results in the specification that Applicants point (pg 47 and Example 4) each concern working examples wherein the mutated protein was expressed in cells. Furthermore, the working examples in the specification wherein a decrease in hematopoietic cell survival was observed all require that the DNA sequence is transfected into hematopoietic cells. However, instant claim 73, as amended, consists solely of a single method step wherein a mutation is made to a protein. In order for hematopoietic cell survival to be regulated (which is the goal of the preamble of the claim), this mutated protein must be expressed in a cell in some manner such that hematopoietic cell survival is affected. The method is missing an essential step(s) wherein the mutated protein is expressed in cell(s) in a manner that results in a decrease in hematopoietic cell survival.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 73-79 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Smith et al (1997. The EMBO Journal. Vol 16(3): 451-464; cited as reference #8 on the 10/6/03 IDS). This rejection was set forth at pg 9-10 of the 10/2/06 Office Action.

Applicants' arguments (2/2/07; pg 7-8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In the response, Applicants argue that Smith does not anticipate the claimed invention. Applicants submit that Smith teaches deletion of segments of the β-chain but does not specifically indicate the importance of the claimed HSRSLP sequence (residues 598-603 of SEQ ID NO: 1). Applicants argue that Smith does not disclose or suggest the claimed binding motif having an amino acid sequence according to SEQ ID

NO: 1 and one or more mutations in the HSRSLP sequence. Applicant argue that the length of the amino acid sequence according to SEQ ID NO: 1 is largely maintained despite the claimed mutation(s) of HSRSLP sequence.

Applicants' arguments have been fully considered but are not found persuasive. It is true that Smith does not teach the importance of the HSRSLP sequence (residues 598-603 of SEQ ID NO: 1). However, while Applicants argue that in the instant invention that the length of SEQ ID NO: 1 is largely maintained, the claims do not include such a limitation. Furthermore, the instant specification does not provide a limiting definition of the phrase "mutating at least one of the residues" and therefore the term has been interpreted to encompass any deletion, addition or substitution of the specified residues. Therefore, claim 73 encompasses a method step wherein any mutation is made to at least one residue of the HSRSLP sequence, including mutations that are deletions of one or more of the HSRSLP residues. As set forth previously, Smith teaches a truncated β-chain ending at residue 541 (out of 897 residues; see Figure 1). The numbering system of Smith includes the leader sequence found in the β-chain (see pg 452, right column). Therefore, the residues in Smith correspond to those used in SEQ ID NO: 1 of the instant application and the truncated β-chain taught by Smith includes a deletion of residues 598-603 of the wild type receptor. Therefore, the truncated β-chain inherently meets the definition of a "mutating at least one of a binding motif" that is the HSRSLP sequence found within SEQ ID NO: 1.

Applicants have amended the preamble of claim 73 to recite "a method of inhibiting hematopoietic cell survival". It is noted that the preamble of claim 73 (as well as dependent claims 74-79) is interpreted as an intended use and bears no accorded patentable weight to distinguish the claims from the method taught by the prior art. Therefore, claim 73 encompasses any method that comprises the step of "mutating at least one of the residues of a binding motif" wherein the receptor has a β-chain of SEQ ID NO: 1, and the binding motif has the sequence ^{598}HSRSLP^{603}. As set forth above, Smith teaches such a method and therefore anticipates instant claim 73. However, Smith also demonstrates (pg 454; Figure 3) that this truncated receptor does not support growth of transfected CTLL2 cells (which meet the limitation of hematopoietic

cells), whereas the full-length receptor does. Therefore, the truncated receptor inhibits hematopoietic cell survival. Therefore, Smith also teaches a method with the same intended use as claim 73.

As amended, claim 74 encompasses a method of claim 73, wherein a serine residue at position 601 is mutated. A mutation of said residue includes a deletion of said residue. As set forth above, the truncated receptor taught by Smith includes a deletion of all residues after 541; therefore, the receptor inherently includes a deletion of residues 601. Therefore, Smith anticipates claim 74 for the same reason as claim 73.

As amended, claim 75 encompasses a method of claim 73, wherein at least two amino acids at any position from 598-603 are mutated. A mutation of said residues includes a deletion of said residues. As set forth above, the truncated receptor taught by Smith includes a deletion of all residues after 541; therefore, the receptor inherently includes at least two deletions of residues 598-603. Therefore, Smith anticipates claim 75 for the same reason as claim 73.

Claim 76 limits the hematopoietic cell of claim 73 to a leukocyte. CTLL2 cells are T cells, which are a "species" of leukocyte (white blood cell). Therefore, the teachings of Smith described above also clearly anticipate claim 76.

As truncation of the receptor β-chain removes each of the residues of the binding motif (598-603), it inherently inhibits phosphorylation of the binding motif. Therefore, the teachings of Smith described above also clearly anticipate claims 77-79.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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